

IN THE SPECIFICATION

On page 1, after the title, add the following paragraph.

This is a continuation of application Serial No. 10/136,666, filed April 30, 2002, which was a continuation of application Serial No. 09/900,390, filed July 6, 2001, which was a continuation of 09/393,581, filed September 9, 1999, which issued as U.S. Patent No. 6,261,536, which was a continuation of application Serial No. 08/794,311, filed February 3, 1997, which issued as U.S. Patent No. 6,066,309; which was a continuation-in-part of application Serial No. 08/794,270, filed January 31, 1997, abandoned, and which claimed priority under 35 U.S.C. '119(e) of U.S. Provisional Application No. 60/011,027, filed February 2, 1996. Each of these prior applications is hereby incorporated herein by reference, in its entirety.

At page 6, lines 18-24, please amend as follows.

FIGURES 1A and 1B

Figure 1A is an elution profile of Re-188-RC-160- labeled with 65 mCi of Re-188 at 6 hours post-labeling from a C₁₈-reverse-phase HPLC column. The y-axis in arbitrary units. Figure 1B is an elution profile of Re-188-RC-160 from a C₁₈-SepPak column using a step-gradient of acidified ethanol.

FIGURES 2A and 2B

Comparative elutions profiles of Re-188-RC-160 radiolabeled at either 90°C or 37°C.

At page 7, lines 6-17, please amend as follows.

FIGURES 8A and 8B

Comparative elution profiles of Re-188-RC-160 with ascorbate added after the radiolabeling (top) or before the radiolabeling (bottom). Both preparations were radiolabeled with 10 mCi (370 Mbq) of Re-188.

FIGURES 9A and 9B

Labeling of a RhoMed radiopharmaceutical product known as LeuTec-MTM, a ^{99m}Tc -labeled anti-SSEA- I antibody. (This product is referred to as “Leuko-I” in Figure 9, which is a summary of the test results from a lot of LeuTecMTM manufactured by RhoMed.) This data shows the difference in radiolabeling yields between unstabilized and stabilized (with ascorbate) product.

FIGURES 10A, 10B and 10C

HPLC profile on ^{99m}Tc -labeled IgM samples showing the difference in yield over time with labeling occurring in the presence of ascorbate or with postlabeling addition of ascorbate.

At page 12, line 31 - page 14, line 12, please amend as follows.

Radiolabeling kits were prepared using aseptic techniques, with each kit prepared in a 10 ml serum vial using a 2 ml liquid fill. The liquid fill contained 200 μg of RC-160 peptide in 45 mM sodium potassium tartrate, 10 mM potassium hydrogen phthalate buffer, pH 5.0, in 5 mM stannous tartrate with 1% maltose added as a freeze-drying excipient. Each kit contained a maximum of 1.19 μg of tin. After filling, the vials were lyophilized, the head space gas filled with nitrogen, and the vials stoppered and crimped. Lyophilized vials were then stored refrigerated at 2-8°C. To label a kit, 4-5

ml of ^{188}Re -perrhenate solution containing 10-100 mCi was added to the kits, and the kits then heated in a boiling water bath for 30-45 minutes. Following a brief cooling period, 2 ml of ascorbic acid for Injection, U.S.P., was added to the labeled kit through a 0.22 micron filter. Two types of parenteral ascorbate were used with similar results, Ascorbic Acid for Injection, U.S.P., 500 mg/2 ml, and AscorvitTM (a preparation of ascorbate) 100 mg (Jenapharm, Germany). An elution profile from an analytical HPLC at 6-hours post-labeling is shown in Fig. 1A. In this study, RC-160 was radiolabeled at pH 5.0 for 30 minutes at 90°C and ascorbate was added postlabeling. The temperature effect is shown in Figs. 2A and 2B: 19 minutes for 37°C and 21 minutes for 90°C. Also shown in Fig. 1B is an elution profile of Re-188-RC 160 from a C18 column using a step-gradient of acidified ethenol. The results are consistent with the HPLC. ^{188}Re -RC-160 to which ascorbate was not added was found to be stable for only up to two hours post-labeling; however, after that the ^{188}Re began to uncouple from the peptide as determined by TLC (using silica-coated thin layer chromatography strips) and confirmed by RP-HPLC (analytical reverse phase HPLC using a C18 column eluted with a continuous gradient of acetonitrile and analyzed by a post-column radioisotope detector, generally at a flow rate of 1 ml/minute). This uncoupling occurred with ^{188}Re , but not with Tc- 99m when used in the same amounts, 20 mCi, suggesting the effect was specific to rhenium at this particular concentration. Post-labeling addition of ascorbate was found to essentially eliminate the uncoupling and stabilize the ^{188}Re -RC-160. Fig. 6. An HPLC profile at 30 hours post-labeling with 65 mCi of ^{188}Re to which ascorbate was added after labeling demonstrated that very little free rhenium could be found. Fig. 7 and Figs. 1A and 1B. Cysteine displacement studies demonstrated that the Re-peptide bond strength was not altered by addition of the ascorbate post-labeling. Briefly, aliquots of 100 μl cysteine dissolved in phosphate buffer saline (pH 7.4 with 1 M

NaOH) were diluted in separate microfuge tubes to result in a doubling dilution. 100 µl of Re188-RC-160 was added to each tube and mixed by inversion. The samples were incubated at 45 minutes at 37°C or 90°C. A 10 µl aliquot of each sample was then spotted on heat-treated ITLC strip and chromatographed in PBS, pH 7.4 until the solvent was 0.5 cm from the strip top. The amount of displacement was expressed as % of total radioactivity at the solvent front. The results for two experiments conducted respectively at 37°C and 90°C are shown at Fig. 3. In a related manner, comparative biodistribution profiles of Re-188-RC-160 at 2 hours post injection into the tail vein of adult, female BALB/c mice (~25g weight) (n5/group) with each animal receiving 0.2 ml containing approximately 4 µCi. Selected organs as shown in Fig. 4 were resected and weighed and the associated radioactivity was determined as a percentage of injected dose pr gram of tissue. The percent dose from blood, bone and muscle was calculated assuming 7, 8.2 and 40% of total body weight for these tissues. 37°C and 90°C were the two temperatures at which radio labeling was performed.

At page 18, lines 1-8, please amend as follows.

Data are presented in Figs. 9A and 9B relating to the labeling of a RhoMed radiopharmaceutical product known as LeuTec-MTM, a ^{99m}Tc-labeled anti-SSEA- I antibody. (This product is referred to as "Leuko- I" in Figs. 9A and 9B, which are a summary of the test results from a lot of LeuTec-MTM manufactured by RhoMed.) This data shows the difference in radiolabeling yields between unstabilized and stabilized (with ascorbate) product. This data, especially that circled and marked "added post-labeling", shows that the composition tends to remain more stable than those compositions where other diluents were used.

At page 18, lines 24-31, please amend as follows.

The inclusion of ascorbic acid into four different preparations of this IgG antibody, prior to technetium labeling, adversely affects labeling yields, blood levels, and the resistance of the labeled antibody to challenge with cysteine. Ascorbic acid was not added to any of the preparations after labeling, since that was not the intent of these particular experiments. Figs. 10A - 10C show HPLC profiles of ^{99m}Tc -labeled IgM samples, showing the difference in yield over time with labeling occurring in the presence of ascorbate on the one hand, and addition of ascorbate post-labeling on the other.